

What is claimed is:

1. A method for treating atherosclerosis which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of an aP2 5 inhibitor.

2. The method as defined in Claim 1 wherein the aP2 inhibitor binds to the aP2 protein and inhibits its function and/or its ability to bind free fatty acids.

3. The method as defined in Claim 1 wherein the aP2 inhibitor contains a hydrogen bond donor or acceptor group and interacts directly or through an intervening water molecule either by ionic or hydrogen bonding interactions, with one, two, or three of the three amino acid residues, designated as Arg 106, Arg 126 and Tyr 128 15 in human aP2 within the aP2 protein.

4. The method as defined in Claim 3 wherein the hydrogen bond donor or acceptor group is acid in nature.

5. The method as defined in Claim 3 where said aP2 inhibitor contains an additional substituent which binds to 20 (in) and/or interacts with a discrete pocket within the aP2 protein defined roughly by the amino acid residues Phe 16, Tyr 19, Met 20, Val 23, Val 25, Ala 33, Phe 57, Thr 74, Ala 75, Asp 76, Arg 78 in human aP2.

6. The method as defined in Claim 5 wherein said 25 additional substituent in said aP2 inhibitor is hydrophobic in nature.

7. The method as defined in Claim 5 in which the through space distance from the hydrogen bond donor/acceptor group and the additional substituent group 30 in said aP2 inhibitor is within the distance of about 7 to about 15 Angstroms.

8. The method as defined in Claim 1 wherein Type II diabetes is treated.

9. The method as defined in Claim 1 wherein the aP2 inhibitor is employed in the form of a pharmaceutically acceptable salt thereof or a prodrug ester thereof.

, 10. The method as defined in Claim 1 wherein the
5 aP2 inhibitor includes an oxazole or analogous ring, a pyrimidine derivative or a pyridazinone derivative.

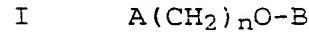
11. The method as defined in Claim 10 wherein the
aP2 inhibitor is a substituted benzoyl or biphenyl-2-
oxazole-alkanoic acid derivative, an oxazole derivative, a
10 2-thio-4,5-diphenyloxazole S-derivative, a phenyl-
heterocyclic oxazole derivative, a diaryloxazole
derivative, a 4,5-diphenyloxazole derivative, an oxazole
carboxylic acid derivative, a phenyloxazolyloxazole
derivative, or a 2-(4,5-diaryl)-2-oxazolyl substituted
15 phenoxyalkanoic acid derivative.

12. The method as defined in Claim 10 wherein the
aP2 inhibitor is a 2-benzyloxypyrimidine derivative, a
dihydro(alkylthio)(naphthylmethyl)oxypyrimidine derivative,
a thiouracil derivative, or an α -substituted pyrimidine-
20 thioalkyl or alkyl ether derivative.

13. The method as defined in Claim 10 wherein the
aP2 inhibitor is a pyridazinone acetic acid derivative.

14. The method as defined in Claim 10 wherein the
aP2 inhibitor is

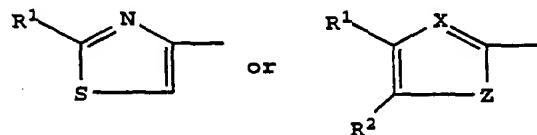
25 (I) a substituted benzoylbenzene or biphenyl alkanoic
acid derivative having the structure:



wherein

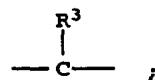
A is a group having the formula

30

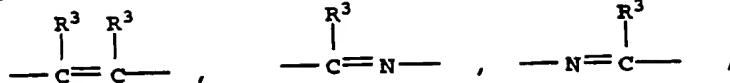


wherein

X is -N- or



Z is



5 R¹ is hydrogen, lower alkyl or phenyl;

R² is hydrogen or lower alkyl; or

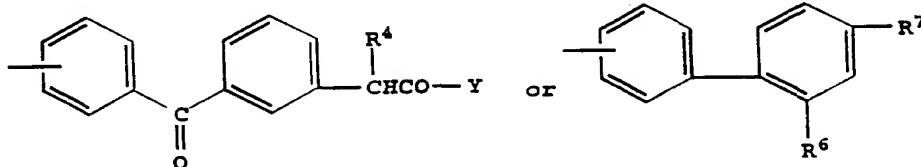
R¹ and R² taken together form a benzene ring, with the proviso that when X is -N-, Z is other than

10 $\begin{array}{c} \text{R}^3 \quad \text{R}^3 \\ | \quad \quad | \\ \text{---} \text{C} = \text{C} \text{---} \end{array} ;$

R³ is hydrogen or lower alkyl;

n is 1-2;

B is



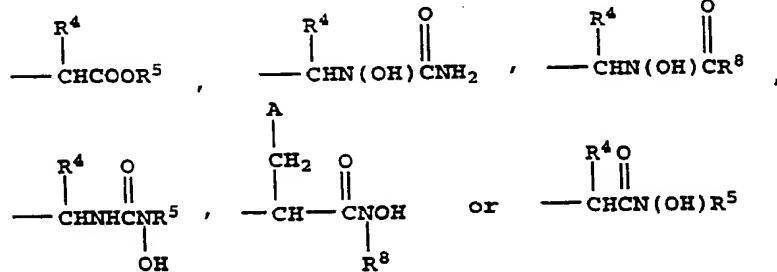
15 wherein

Y is OR⁵ or N(OH)R⁸;

R⁴ and R⁵ are each, independently, hydrogen or lower alkyl;

R⁶ is hydrogen, halo or nitro;

20 R⁷ is



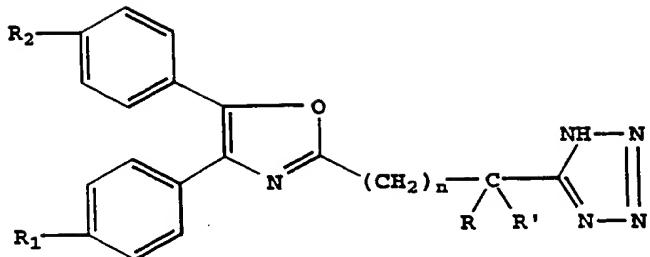
R⁸ is lower alkyl;

m is 0-3;

25 or a pharmacologically acceptable salts thereof;

(II) oxazole derivatives which have the structure

II



in which;

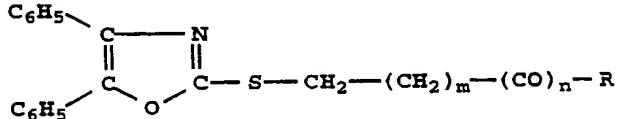
5 R and R' are identical or different and represent a hydrogen atom or an alkyl radical containing 1 or 2 carbon atoms,

10 R₁ and R₂ are identical or different and represent hydrogen or halogen atoms or alkyloxy radicals in which the alkyl portion contains 1 to 4 carbon atoms in a straight or branched chain, and

n equals 3 to 6, as well to their salts;

(III) 2-thiol-4,5-diphenyloxazole S-derivatives which have the structure

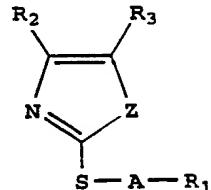
III



15 wherein m is 0, 1 or 2, n is 1 and R represents hydroxy, alkoxy or amino, and pharmaceutically acceptable addition salts thereof;

(IV) azole derivatives of the structure

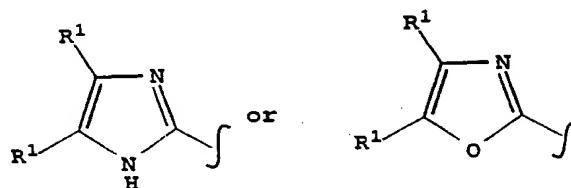
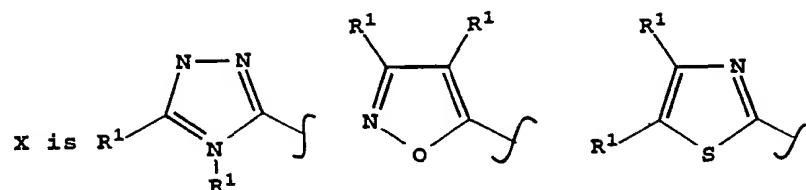
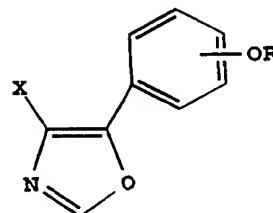
20 IV



wherein R₁ is carboxyl, esterified carboxyl or other functionally modified carboxyl group; R₂ and R₃ each are aryl of up to 10 carbon atoms; A is C_nH_{2n} in which n is an integer from 1 to 10, inclusive; and Z is O or S, and physiologically acceptable salts thereof;

(V) phenyl-heterocyclic oxazole derivatives which have the structure

V



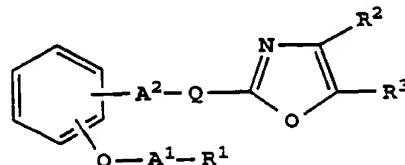
5

R is CH_2R^2 ; R^1 is Ph or Th; R^2 is CO_2R^3 ; and10 R^3 is H, or $\text{C}_1\text{-C}_4$ lower alkyl;

or pharmaceutically acceptable salt thereof;

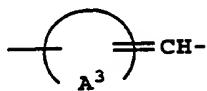
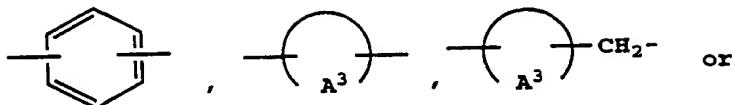
(VI) diaryloxazole derivatives having the structure

VI

15 wherein R^1 is carboxy or protected carboxy, R^2 is aryl, R^3 is aryl, A^1 is lower alkylene,

A² is bond or lower alkylene and

-Q- is

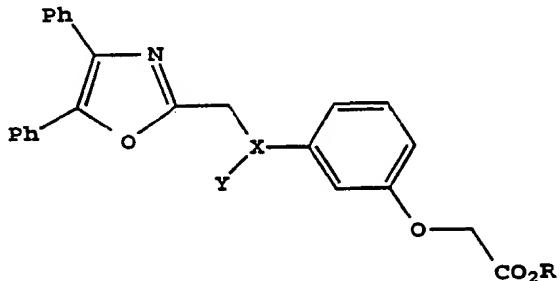


(in which A³ is cyclo (lower)alkane or
cycle(lower)alkene,

5

each of which may have suitable substituent(s));
(VII) 4,5-diphenyloxazole derivatives having the
structure

VIIA



10

wherein

R is H or C₁-C₅ lower alkyl,

X is N or CH,

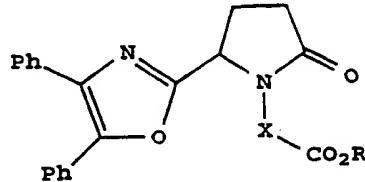
Y is H or CO₂R¹, or COR², provided that when X is CH,

15 Y is not H,

R¹ is C₁-C₅ lower alkyl, or phenylmethyl, and

R² is C₁-C₅ alkyl;

VIIIB

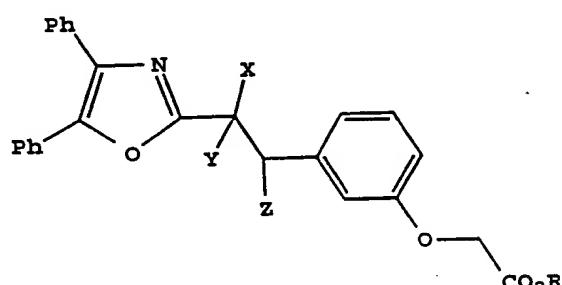


20 wherein

R is H or C₁-C₅ lower alkyl,

X is $(CH_2)_n$ or para or meta substituted phenyl
 wherein the substituent is OR^2 ,
 R² is C₁-C₅ alkyl, and
 n is an integer of 4 to 8,
 5 and pharmaceutically acceptable salts thereof;
 (VIII) oxazole carboxylic acid derivatives having
 the structure

VIII



10

wherein

Y and Z are independently hydrogen or together form
 a bond;

X is CN, CO_2R^1 or $CONR^2R^3$;

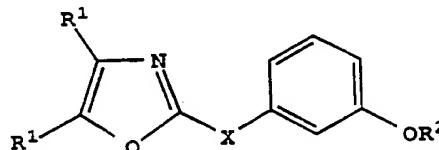
15 R and R¹ are independently or together H, Na, or
 C₁-C₅ lower alkyl;

R² and R³ are independently or together H, or C₁-C₅
 lower alkyl;

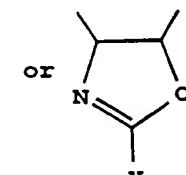
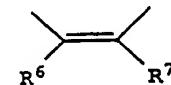
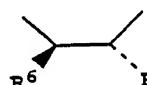
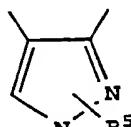
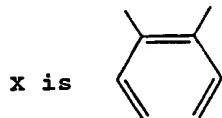
or alkali metal salt thereof;

20 (IX) phenyloxazolyloxazole derivatives having the
 structure

IX

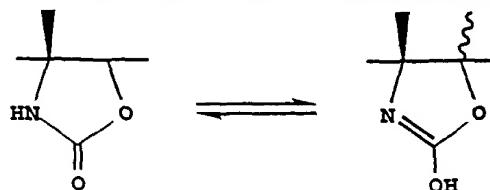


wherein



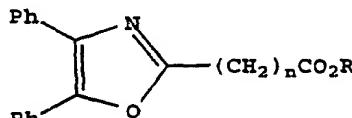
25

Y is CH_3 , Ph, or OH, provided that when Y is OH, the compound exists in the keto-enol tautomerism form

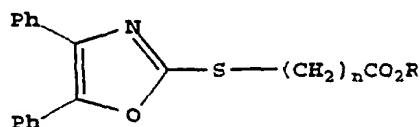


5 R^1 is Ph or Th;
 R² is CH_2R^3 ;
 R³ is CO_2R^4 ;
 R⁴ is H or $\text{C}_1\text{-C}_5$ lower alkyl;
 R⁵ is H or CH_3 ; R⁶ is OHCHN or H_2N ; and
 R⁷ is H or OH;
 10 or pharmaceutically acceptable salt thereof;
 (X) 2-(4,5-diaryl)-2-oxazolyl substituted
 phenoxyalkanoic acids and esters having the structure

XA

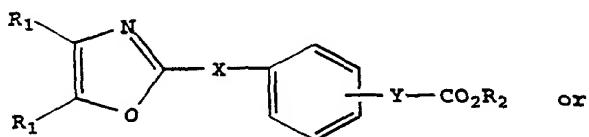


15 XB



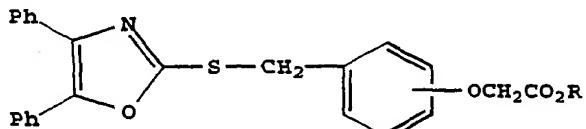
(wherein n is 7-9 and R is hydrogen or lower alkyl; or when R is hydrogen, the alkali metal salt thereof),

XC



20

XD



wherein

R₁ is phenyl or thiienyl;

R₂ is hydrogen, lower alkyl or together with CO₂ is tetrazol-1-yl;

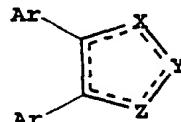
X is a divalent connecting group selected from the group consisting of CH₂CH₂, CH=CH, and CH₂O;

5 Y is a divalent connecting group attached to the 3- or 4-phenyl position selected from the group consisting of OCH₂, CH₂CH₂ and CH=CH,

or when R₂ is hydrogen, an alkali metal salt thereof;

10 (XI) substituted 4,5-diaryl heterocycles having the formula

XI



in which

15 each group Ar is the same or different and is optionally substituted phenyl or optionally substituted heteroaryl;

X is nitrogen or CR¹;

Y is nitrogen, N(CH₂)_nA or C(CH₂)_nA;

Z is nitrogen, oxygen or N(CH₂)_nA, and the dotted

20 line indicates the optional presence of a double bond so as to form a fully unsaturated heterocyclic ring;

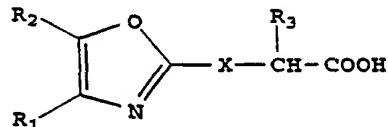
R¹ is hydrogen, C₁₋₄alkyl, optionally substituted phenyl or optionally substituted heteroaryl;

n is 4 to 12; and

25 A is CO₂H or a group hydrolysable to CO₂H, 5-tetrazolyl, SO₃H, P(O)(OR)₂, P(O)(OH)₂, or P(O)(R)(OR) in which R is hydrogen or C₁₋₄alkyl, or a pharmaceutically acceptable salt thereof;

(XII) compounds which have the structure

30 XII



Where X is O or S;

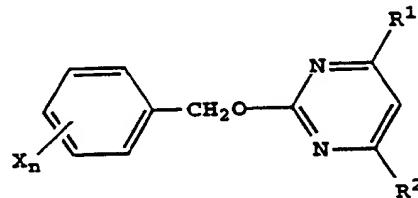
R₁ is H, phenyl or phenyl substituted with F, Cl or Br or alkoxy,

R₂ is H, alkyl, phenyl or phenyl substituted with F, Cl or Br or alkoxy, and

5 R₃ is H or alkyl;

(XIII) 2-benzyloxypyrimidine derivatives having the following structure

XIII



10 wherein

R¹ and R² are each independently H, a halogen, hydroxyl, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₃-C₅ alkenyl, C₃-C₅ alkynyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₃-C₅ alkenyloxy, C₃-C₅ alkynyloxy, C₁-C₄ alkylthio, or phenyl, with the

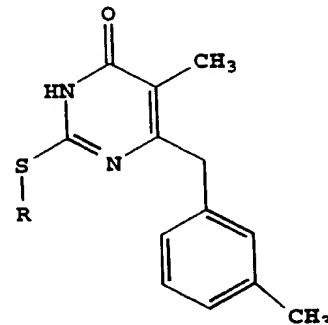
15 proviso that at least one of R¹ and R² must be hydroxyl; n is an integer of 0 to 5; and

each X which may be identical or different if n is greater than 1, is a halogen, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylthio, C₇-C₉ aralkyloxy, phenyl,

20 hydroxymethyl, hydroxycarbonyl, C₁-C₄ alkoxy carbonyl, or nitro;

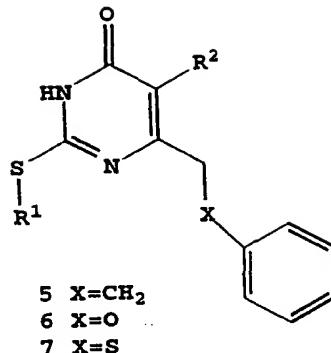
(XIV) dihydro(alkylthio)-(naphthylmethyl)-oxopyrimidines which have the structures

XIVA

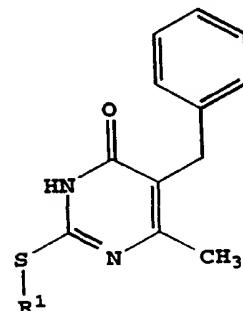


3a R=sec-butyl
3b R=cyclopentyl
3c R=cyclohexyl

XIVB

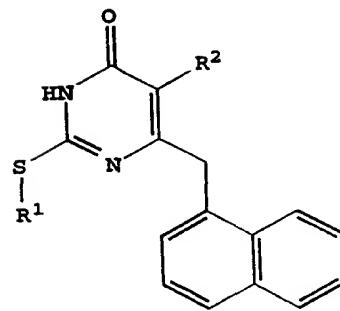


XIVC

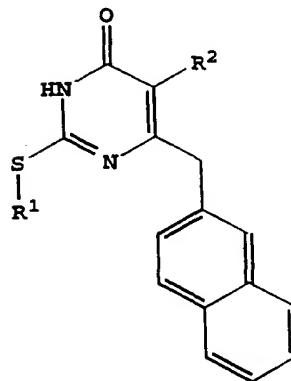


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XIVD



XIVE

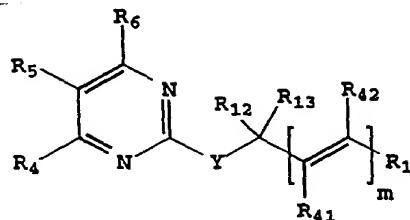


R^1 = sec-butyl, cyclopentyl, cyclohexyl;

10 R^2 = H, CH_3 , including tautomers of the above;

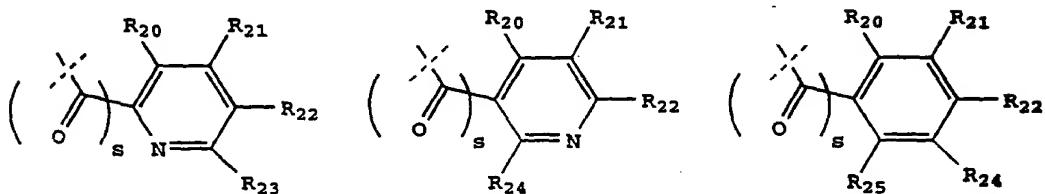
(XVI) α -substituted pyrimidine-thioalkyl and
alkylether compounds which have the structure

XVI



5 where m is 0 or 1;

R^1 is selected from $-CO_2R_{53}$, $-CONR_{54}R_{55}$,



where s is 0 or 1, and R_{20} , R_{21} , R_{22} , R_{23} , R_{24} , and R_{25} are

10 the same or different and are selected from -H, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_3-C_8 cycloalkyl, $-CF_3$, $-NO_2$, -halo, $-OH$, $-CN$, phenyl, phenylthio, -styryl, $-CO_2(R_{31})$, $-CON(R_{31})(R_{32})$, $-CO(R_{31})$, $-(CH_2)_n-N(R_{31})(R_{32})$, $-C(OH)(R_{31})(R_{33})$, $-(CH_2)_nN(R_{31})(CO(R_{33}))$, $-(CH_2)_nN(R_{31})(SO_2(R_{33}))$, or where R_{20} and R_{21} , or R_{21} and R_{22} , or R_{22} and R_{23} are taken together to form a five or six-membered saturated or unsaturated ring containing 0 or 1 oxygen, nitrogen or sulfur, where the unsaturated ring may be optionally substituted with 1, 2 or 3, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-OH$, $-CH_2OH$, $-(CH_2)_n-N(R_{31})(R_{32})$, $-C_3-C_8$ cycloalkyl, $-CF_3$, -halo, $CO_2(R_{31})$, $-CON(R_{31})(R_{32})$, $-CO(R_{31})$, $-(CH_2)_nN(R_{31})(CO(R_{33}))$, $-(CH_2)_nN(R_{31})(SO_2(R_{33}))$, $-CN$, $-CH_2CF_3$ or $-CH(CF_3)_2$, or phenyl and the saturated ring may be optionally substituted with 1, 2 or 3, $-C_1-C_6$ alkyl, $-C_1-C_6$ alkoxy, $-OH$, $-CH_2OH$ or $-(CH_2)_n-N(R_{31})(R_{32})$ or one oxo ($=O$);

15 where n is 0-3 and R_{31} , R_{32} and R_{33} are the same or different and are selected from

20 $-H$,

25 C_1-C_6 alkyl,

phenyl optionally substituted with 1, 2 or 3 -halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, -CF₃, -OH or -CN,
or where R₃₁ and R₃₂ taken together with the attached
nitrogen to form a ring selected from -pyrrolidinyl, -

5 piperidinyl, -4-morpholinyl, -4-thiomorpholinyl, -4-
piperazinyl, -4-(1-C₁-C₆alkyl)piperazinyl, or a member
selected from
1-cyclohexenyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-
pyrimidinyl, 2-imidazolyl, 4-imidazolyl, 2-benzothiazolyl,
10 2-benzoxazolyl, 2-benzimidazolyl, 2-oxazolyl, 4-oxazolyl,
2-thiazolyl, 3-isoxazolyl, 5-isoxazolyl, 5-methyl-3-
isoxazolyl, 5-phenyl-3-isoxazolyl, 4-thiazolyl, 3-methyl-2-
pyrazinyl, 5-methyl-2-pyrazinyl, 6-methyl-2-pyrazinyl, 5-
chloro-2-thienyl, 3-furyl, benzofuran-2-yl, benzothien-2-
15 yl, 2H-1-benzopyran-3-yl, 2,3-dihydrobenzopyran-5-yl, 1-
methylimidazol-2-yl, quinoxalin-2-yl, piperon-5-yl, 4,7-
dichlorobenzoxazol-2-yl, 4,6-dimethylpyrimidin-2-yl, 4-
methylpyrimidin-2-yl, 2,4-dimethylpyrimidin-6-yl, 2-
methylpyrimidin-4-yl, 4-methylpyrimidin-6-yl, 6-
20 chloropiperon-5-yl, 5-chloroimidazol[1,2-a]pyridin-2-yl, 1-
H-inden-3-yl, 1-H-2-methyl-inden-2-yl, 3,4-dihydronaphth-1-
yl, S-4-isopropenylcyclohexen-1-yl or 4-dihydronaphth-2-yl;
where R₅₃ is selected from -H, C₁-C₆alkyl, C₃-
C₆cycloalkyl, phenyl (optionally substituted with 1, 2, or
25 3 -halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, -CF₃, -OH, -CN), or a
five or six-membered unsaturated ring containing 0 or 1
oxygen, nitrogen or sulfur, where the unsaturated ring may
be optionally substituted with -H, C₁-C₆ alkyl, C₁-C₆
alkoxy, -OH, -CH₂OH, or -(CH₂)_n-N(R₃₁)(R₃₂);
30 where R₅₄ and R₅₅ being the same or different are
selected from -H, C₁-C₆ alkyl, allyl, or phenyl (optionally
substituted with 1, 2 or 3 -halo, C₁-C₆ alkyl, C₁-C₆ alkoxy
or -CF₃), or taken together with the attached nitrogen to
form a ring selected from -pyrrolidinyl, -piperidinyl, -4-
35 morpholinyl, -4-thiomorpholinyl, -4-piperazinyl, -4-(1-C₁-
C₆alkyl)piperazinyl;

R₄₁ and R₄₂, being the same or different, are selected from -H and C₁-C₄ alkyl;

R₁₂ is selected from -H, C₁-C₆ alkyl, -C₃-C₆ cycloalkyl, -CN, -C(O)NH₂, -C(O)N(C₁-C₆alkyl)(C₁-C₆alkyl), -

5 CO₂H, -CO₂(C₁-C₆alkyl), -CH₂OH, -CH₂NH₂ or -CF₃;

R₁₃ is selected from -H, C₁-C₆ alkyl or -CF₃;

y is selected from -S-, -S(O)-, -S(O)₂, or -O-;

R₄ is -OH;

R₅ is selected -H, -C₂H₄OH, -C₂H₄-O-TBDMS, halo, -C₃-C₆ cycloalkyl, C₁-C₃ alkoxy, -CH₂CH₂Cl or C₁-C₄ alkyl, with the proviso that R₅ is not isobutyl;

10 or, when R₆ is hydroxyl, R₄ and R₅ are taken together to form a five or six-membered saturated or unsaturated ring which together with the pyrimidine ring form the group consisting of 7H-pyrrolo[2,3-d]pyrimidine, 5,6-dihydro-7H-pyrrolo[2,3-d]pyrimidine, furo[2,3-d]pyrimidine, 5,6-dihydro-furo[2,3-d]pyrimidine, thieno[2,3-d]pyrimidine, 5,6-dihydro-thieno[2,3-d]pyrimidine, 1H-pyrazolo[3,4-d]pyrimidine, 1H-purine, pyrimido[4,5-d]pyrimidine, 20 pteridine, pyrido[2,3-d]pyrimidine, or quinazoline, where the unsaturated ring may be optionally substituted with 1, 2 or 3, C₁-C₆ alkyl C₁-C₆ alkoxy, -OH, -CH₂OH, or -(CH₂)_n-N(R₃₁)(R₃₂), -C₃-C₈ cycloalkyl, -CF₃, -halo, -CO₂(R₃₁), -CON(R₃₁)(R₃₂), -CO(R₃₁), -(CH₂)_nN(R₃₁)(CO(R₃₃)), -CON(R₃₁)(SO₂(R₃₃)), and the saturated ring may be optionally substituted with 1, 2 or 3, -C₁-C₆ alkyl, C₁-C₆ alkoxy, -OH, -CH₂OH, or -(CH₂)_n-N(R₃₁)(R₃₂) or one oxo (=O); and

25 R₆ is selected from -H, -OH, halo, -CN, -CF₃, -CO₂(R₆₁), -C(O)R₆₁ or -C(O)N(R₆₁)(R₆₂) where R₆₁ and R₆₂ are the same or different and are selected from

-H,

C₁-C₆ alkyl,

phenyl optionally substituted with 1, 2 or 3 -halo,

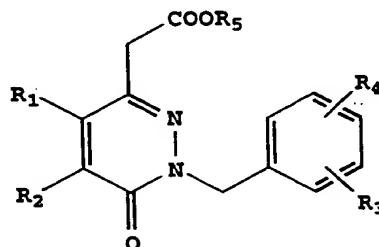
35 C₁-C₆ alkyl, C₁-C₆ alkoxy, -CF₃, -OH, -CN,

or where R₆₁ and R₆₂ taken together with the attached nitrogen to form a ring selected from -pyrrolidinyl, -

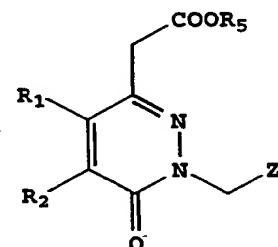
piperidinyl, -4-morpholinyl, -4-thiomorpholinyl, -4-piperazinyl, or -4-(C₁-C₆ alkyl)piperazinyl;

pharmaceutically acceptable salts, hydrates, N-oxides and solvates thereof;

5 (XVII) compounds which have the structure



XVIIA



XVIIIB

where R₁ and R₂ are H, alkyl, aryl or arylalkyl, where the alkyl can include as substituents halogen, CF₃, CH₃O, CH₃S, 10 NO₂, or R₁ and R₂ with the carbons to which they are attached can form methylenedioxy, or

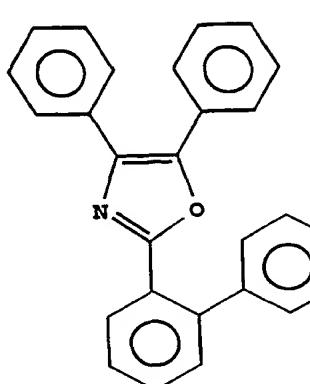
R₁ and R₂ can form a C₃-C₇ non-aromatic ring, or a heterocycle which can be pyridine, pyrazine, pyrimidine, pyridazine, indol, or pyrazole, or an oxygen containing 15 heterocycle which can be pyran or furan, or a sulfur containing heterocycle which can be thiopyran, or thiophene; the heterocycles being optionally substituted with halogen or alkyl,

20 R₃ and R₄ are H, alkyl, halogen, CF₃, CH₃O, CH₃S or NO₂ or R₃ and R₄ with the carbons to which they are attached can form a methylenedioxy group,

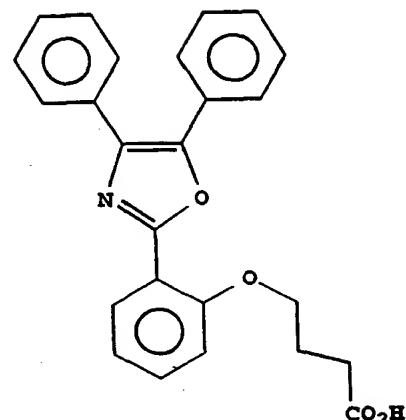
R₅ is H, and

25 Z is a heterocycle which can be pyridine, thiazole, benzothiazole, benzimidazole or quinoline, which Z group can optionally be substituted with halogen or alkyl.

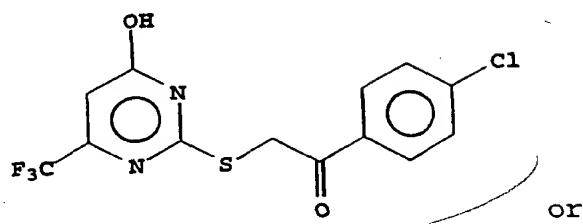
15. The method as defined in Claim 1 wherein the aP2 inhibitor has the structure



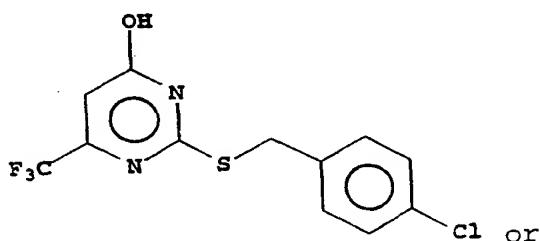
and



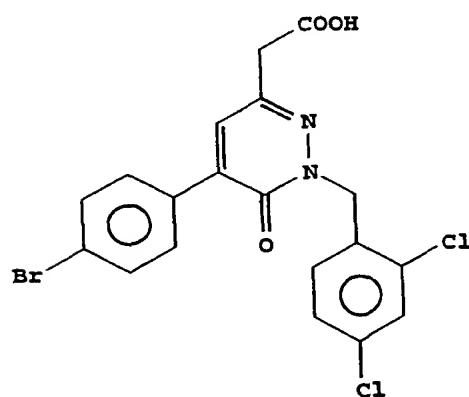
5



or



cl or



10

16. A pharmaceutical combination comprising an aP2 inhibitor and another type antiatherosclerotic agent.

17. The combination as defined in Claim 16 wherien the other antiatherosclerotic agent is an MTP inhibitor, an 5 HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, other cholesterol lowering agent, a lipoxygenase inhibitor, an ACAT inhibitor or a PPAR α/γ dual agonist.

18. The combination as defined in Claim 16 wherien 10 the antiatherosclerotic agent is pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin or fluvastatin.

19. The combination as defined in Claim 16 wherein 15 the aP2 inhibitor is present in a weight ratio to the antiatherosclerotic agent within the range from about 0.01 to about 100:1.

20. A method for treating atherosclerosis which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a pharmaceutical combination as defined in Claim 16.

20